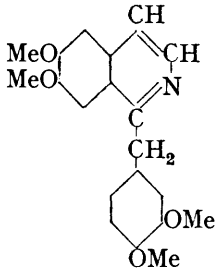
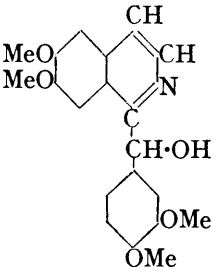
164. α- and β-Hydroxylaudanosines. Part I. Their Preparation from Papaverinol.

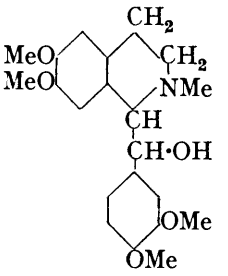
By F. E. King, Philibert L'Ecuyer, and F. L. Pyman.

Although the oxidation of papaverine (I) is usually accompanied by fission of the molecule, two products which retain the original benzyl*iso*quinoline skeleton have been described. These are the secondary alcohol (II) and the related ketone, and they correspond to successive stages in the oxidation of the methylene group. Papaveraldine, the ketone, was the first to be obtained (Goldschmiedt, *Monatsh.*, 1885, **6**, 954), and the alcohol, papaverinol, was at one time known simply as its reduction product (Stuchlik, *ibid.*, 1900, **21**, 813),

but a subsequent direct preparation of (II) from papaverine by the action of mercuric acetate (Gadamer, *Arch. Pharm.*, 1915, **253**, 274) definitely established it as an oxidation product of the alkaloid.


(I.)


(II.)


(III.)

On the other hand, in the parallel tetrahydropapaverine series, of which laudanosine is the most important example, the tendency to cleavage would appear to be appreciably greater (cf. Pyman, J., 1909, **95**, 1266), and oxidation products comparable with papaverinol and papaveraldine are unknown. Accordingly, with the ultimate intention of elucidating the mechanism of the oxidative scission of laudanosine, one of us (F. L. P.) several years ago undertook the reduction of papaverinol methochloride with the idea of preparing hydroxylaudanosine (III). Partly because the addition of hydrogen can create new asymmetric centres, several reduction products, *e.g.*, laudanosine and the stereoisomeric hydroxylaudanosines, *N*-methyl- and hydroxy-*N*-methyl-pavines, were possible. Tin and hydrochloric acid being used as reagents, actually three compounds were isolated, *viz.*, laudanosine, a hydroxylaudanosine, m. p. 138°, and a third base in the form of a *hydrochloride*, m. p. 231° (235° corr.).

The investigation was for a time interrupted at this juncture, but has lately been resumed and considerably simplified by adoption of the method of catalytic reduction. Under the new conditions the main product is the base, m. p. 138° (now designated *α-hydroxylaudanosine*), and by addition of hydrochloric acid to the alcoholic mother-liquors the hydrochloride, m. p. 231°, is obtained. This has been identified as a salt of a second or β-*hydroxylaudanosine*, m. p. 108—109°. No other products are formed during the reduction, and the isolation of the isomerides is therefore relatively simple, the total yield being nearly theoretical.

The two hydroxylaudanosines are now undergoing detailed investigation in a number of directions.

Experimental.

Papaverinol Methochloride.—Metho-salts of papaverinol were prepared by Stuchlik (*loc. cit.*, p. 824), who gives for the methiodide m. p., according to the rate of heating, 188—200°, and for the methochloride m. p. 178—182°, but no analysis. Papaverinol obtained by the method of Gadamer (*loc. cit.*) and recrystallised from alcohol until pure (m. p. 138°; yields, 50—70%) was refluxed with excess of methyl iodide for 4 hours; the methiodide obtained had m. p. varying from 185° to 210°. By digestion at 100° in aqueous-alcoholic solution with silver chloride it was converted into the *methochloride*, which crystallised from alcohol in colourless crusts of prisms, m. p. 205—206° (211—212° corr.) (Found : Cl, 8·5. $C_{21}H_{24}O_5NCl$ requires Cl, 8·7%).

Reduction of Papaverinol Methochloride.—(A) *The action of tin and hydrochloric acid.* A solution of the pure methochloride (48 g.) in alcohol (300 c.c.) was heated on a steam-bath with concentrated hydrochloric acid (100 c.c.) and tinfoil (20 g.). When the metal had dissolved, a second portion (20 g.) was added, together with a further quantity of acid (100 c.c.), and this was followed 2 hours later by a third portion (10 g.), after which the digestion was continued for another 4 hours. The product was then diluted with water, and the tin precipitated with hydrogen sulphide. The solution and washings were evaporated to dryness under reduced pressure, yielding a straw-coloured gum, which was dissolved in water, and after the addition of a slight excess of alkali, the solution was extracted with chloroform. The solvent was evaporated, and the extract (*ca.* 40 g.) dissolved in alcohol (35—40 c.c.) and left for 2 days to crystallise.

The solid which separated (9·6 g., m. p. *ca.* 130°) was contaminated with laudanosine, but crystallisation from 8—10 parts of alcohol gave pure *α-hydroxylaudanosine* (6·6 g.) as colourless stout needles, m. p. 138° (140° corr.) (Found: C, 67·5; H, 7·5. $C_{21}H_{27}O_5N$ requires C, 67·6; H, 7·2%).

The solution from which the crude hydroxylaudanosine had separated was mixed with oxalic acid (12 g.) and kept over-night; crystalline acid oxalates (21 g.) were then deposited. These were decomposed with aqueous sodium hydroxide, which was extracted first with ether and then with chloroform. From the ethereal solution, by evaporation and crystallisation from alcohol, laudanosine (3·2 g., m. p. 110—112°) was isolated, and by dissolving the evaporated chloroform extract in the alcoholic mother-liquor and allowing it to crystallise, a second crop (2·4 g., m. p. 100—102°, undepressed by authentic laudanosine) was recovered. The remaining alcoholic solution when evaporated to dryness yielded a gum, which on solution in a little fairly concentrated hydrochloric acid gave a hydrochloride (4 g.), m. p. 235° (corr.) after crystallisation from 5*N*-acid. A third specimen of laudanosine (1·9 g., m. p. 108°), which was isolated from the side fractions by means of the oxalate, was the only other crystalline product obtained in the course of the separation.

(B) *Catalytic hydrogenation.* Papaverinol methochloride (8 g.), dissolved in aqueous alcohol (30 c.c. of 70%), was reduced by means of hydrogen in the presence of platinum oxide catalyst (0·4 g.). After 4½ hours, when 2 molecules of hydrogen (*ca.* 490 c.c.) had been absorbed, reduction ceased. On filtration and evaporation to dryness under diminished pressure, the solution yielded a crystalline mass of hydrochlorides, which was treated with weak aqueous sodium hydroxide. The product was dissolved in boiling alcohol, and from the cooled solution there separated α-hydroxylaudanosine (5·6 g.), m. p. 136—137°, which afforded by one further crystallisation the pure substance, m. p. 138° alone or mixed with the specimen obtained as in (A).

A specimen of the base dissolved in the minimum amount of methyl alcohol was converted by the addition of alcoholic hydrogen chloride into *α-hydroxylaudanosine hydrochloride*, which crystallised from a small volume of alcohol in colourless prisms, m. p. *ca.* 135° (efferv.) (Found: C, 56·9; H, 7·3; Cl, 7·6. $C_{21}H_{27}O_5N,HCl,2H_2O$ requires C, 56·6; H, 7·2; Cl, 8·0%). The *picrate*, which was prepared by mixing equivalents of the two components in alcoholic solution, was only sparingly soluble in organic solvents. It was conveniently crystallised from dioxan, and formed light yellow prisms, m. p. 198° (decomp.) (Found: N, 9·3. $C_{21}H_{27}O_5N,C_6H_3O_7N_3$ requires N, 9·3%).

The alcoholic solution from which the α-hydroxylaudanosine had originally been crystallised was evaporated under diminished pressure. The syrupy residue showed no immediate tendency to crystallise, and it was therefore dissolved in alcohol (*ca.* 25 c.c.), to which a little alcoholic hydrogen chloride was then added. This caused the separation of *β-hydroxylaudanosine hydrochloride* (1·4 g.), which after a further crystallisation had m. p. 228—230° (efferv.). The pure salt crystallised from a moderate volume of alcohol in clusters of colourless needles, m. p. 231° (efferv.), and was identical with the material of m. p. 235° (corr.) isolated during the earlier experiment (Found: C, 61·2; H, 6·8; Cl, 8·5. $C_{21}H_{27}O_5N,HCl$ requires C, 61·5; H, 6·8; Cl, 8·7%).

An aqueous solution of the hydrochloride was basified, and the resulting white precipitate of *β-hydroxylaudanosine* was crystallised from aqueous alcohol (50%). The pure base formed a voluminous mass of minute needles which softened markedly at 74—75° and finally melted at 100° (efferv.), but after drying in an evacuated desiccator had m. p. 108—109° without previous softening (Found: C, 67·7; H, 7·4. $C_{21}H_{27}O_5N$ requires C, 67·6; H, 7·2%). Neutralisation with picric acid in alcoholic solution afforded the sparingly soluble *picrate*, which crystallised from methyl ethyl ketone in clusters of yellow prisms, m. p. 178—179° (Found: N, 9·4%).

In subsequent experiments a more active catalyst was used: not only was reduction more rapid, but the relative proportions of the two isomerides appeared to be affected. For example, the reduction of 125 g. of papaverinol methochloride, which required 13·8 l. of hydrogen, with the aid of 4·5 g. of catalyst, was complete within 1 hour, and on isolation of the products as already described, there were obtained 61 g. of pure α-hydroxylaudanosine and 40 g. of the β-isomeride, *i.e.*, a ratio of 2 : 1 as compared with 4 : 1 in the first experiment, and an overall yield exceeding 90%.

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The College of Technology, Manchester.
The Dyson Perrins Laboratory, Oxford.

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